CAPS

BY

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Definition:

Antiphospholipid syndrome (APS) is an autoimmune disorder characterised by arterial and venous thrombosis, adverse pregnancy outcomes (for mother and fetus), and raised levels of antiphospholipid (aPL) antibodies.

INFECTIONS

- HIV
- TB
- Syphilis
- Lyme disease
- Infectious Mononucleosis
- Hep. C

DRUGS

- Phenothiazines
- Procainamide
- Chlorpromazine
- Hydralazine
- Phenytoin
- Valproate

Common auto immune diseases ass with APL ab are

- 1.SLE-25-50%
- 2.sjogren's –42%
- 3.RA-33%
- 4.AITP-30%
- 5.AIHA-unknown
- 6.MCD-22%
- 7.behcet-20%

Types :

1. Primary antiphospholipid syndrome

APS occurs in the absence of any other related disease.

2. Secondary antiphospholipid syndrome

APS occuring in the context of other autoimmune diseases, such as systemic lupus erythematosus (SLE).

3. Catastrophic antiphospholipid syndrome

In rare cases, APS leads to rapid organ failure due to generalised thrombosis; this is termed (CAPS) and is associated with a high risk of death.

Table 1

International Consensus Statement on Revised Criteria for Classification of the Antiphospholipid Syndrome (AP

Diagnosis of APS is made when at least one clinical and at least one laboratory criteria are me

Clinical Criteria

1) **Vascular thrombosis**
   a) One or more clinical episodes of arterial, venous, or small-vessel thrombosis any tissue or organ
   b) Thrombosis must be confirmed by imaging or Doppler studies
2) **Pregnancy morbidity**
   a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th wk of gestation
   b) One or more premature births of a morphologically normal neonate at or before the 34th wk of gestation due to preeclampsia, eclampsia, or placenta insufficien
   c) Three or more unexplained consecutive spontaneous abortions before the 10th wk of gestation with maternal anatomic or hormonal abnormalities

Laboratory Criteria†

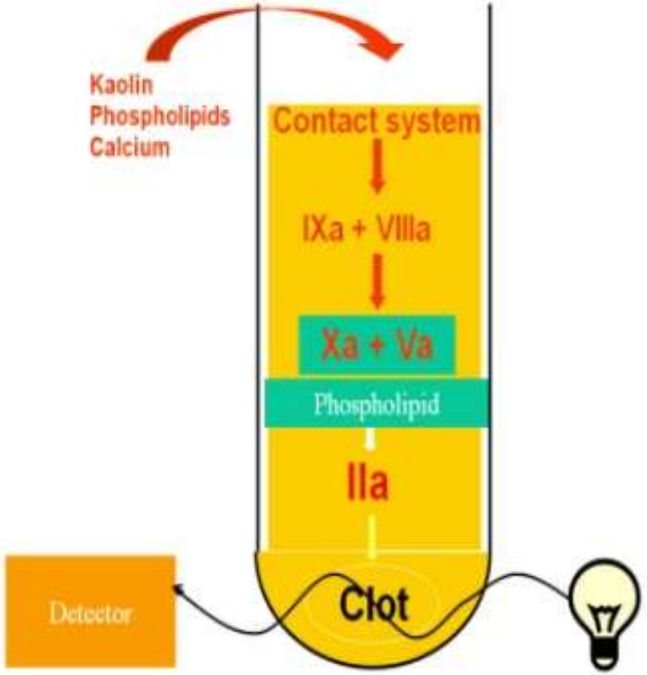
1) **aCL of IgG and/or IgM isotype in serum or plasma present in medium (>40 GPL or MPL) or high titer (>99th percentile)**
   a) Measured by ELISA for β_2GPI-dependent anticardiolipin Ab
2) **LA in serum (detected in the following steps)**
   a) Prolonged phospholipid-dependent coagulation demonstrated on a screening test (e.g., aPTT, dRVVT, dilute prothrombin time)
   b) Failure to correct the prolonged coagulation time by mixing with normal platelet plasma
   c) Shortening/correction of the prolonged coagulation time by adding excess phospholipid
   d) Exclusion of other coagulopathies (factor VIII inhibitor or heparin)
3) **Anti-β_2GPI antibody of IgG and/or IgM isotype in serum or plasma (in titer >99th percentile)**
   a) Measured by standardized ELISA

** Classification of APS should be avoided if less than 12 weeks or more than five years separate t positive aPL test and the clinical manifestation.*

† Present on two or more occasions, at least 12 weeks apart.

aCL: anticardiolipin antibodies; GPL: IgG phospholipid units; MPL: IgM phospholipid units; ELISA: enzyme-linked immunosorbent assay; β_2GPI: β_2-glycoprotein I; LA: lupus anticoagulant; aPTT: activated partial thromboplastin time; dRVVT: dilute Russell viper venom time.

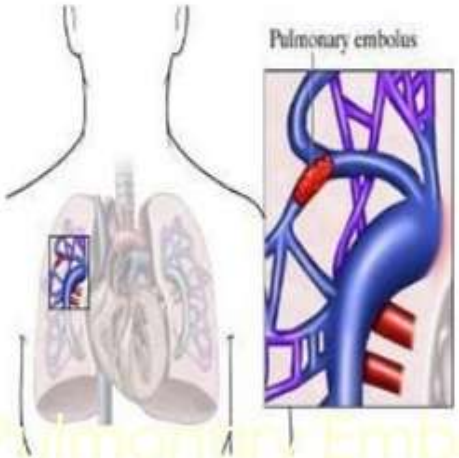
Laboratory diagnosis



Clinical presentation of APS

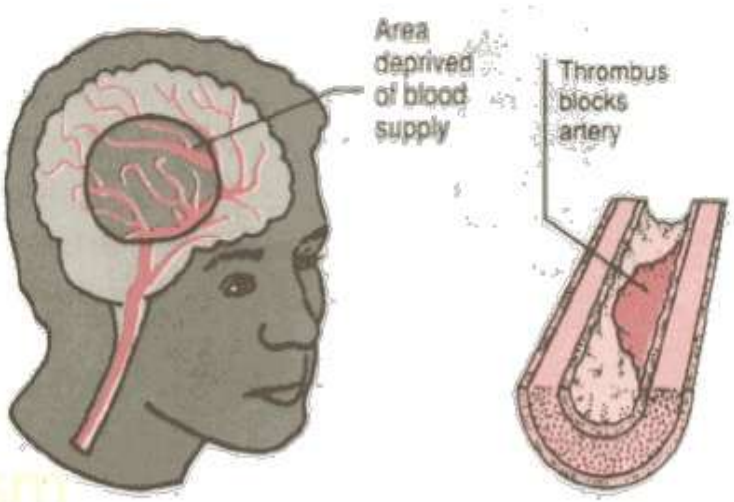
- Venous Thromboembolism:

Deep Vein Thrombosis



Arterial Occlusion:

Stroke and TIAs are the most common



Sydney revision of Sapporo criteria 2006

aPL associated manifestations (individual diagnosis)

- Thrombocytopenia (occurs in up to 50%)
- Cardiac valve disease
- Livedo reticularis
- Nephropathy (late manifestation)

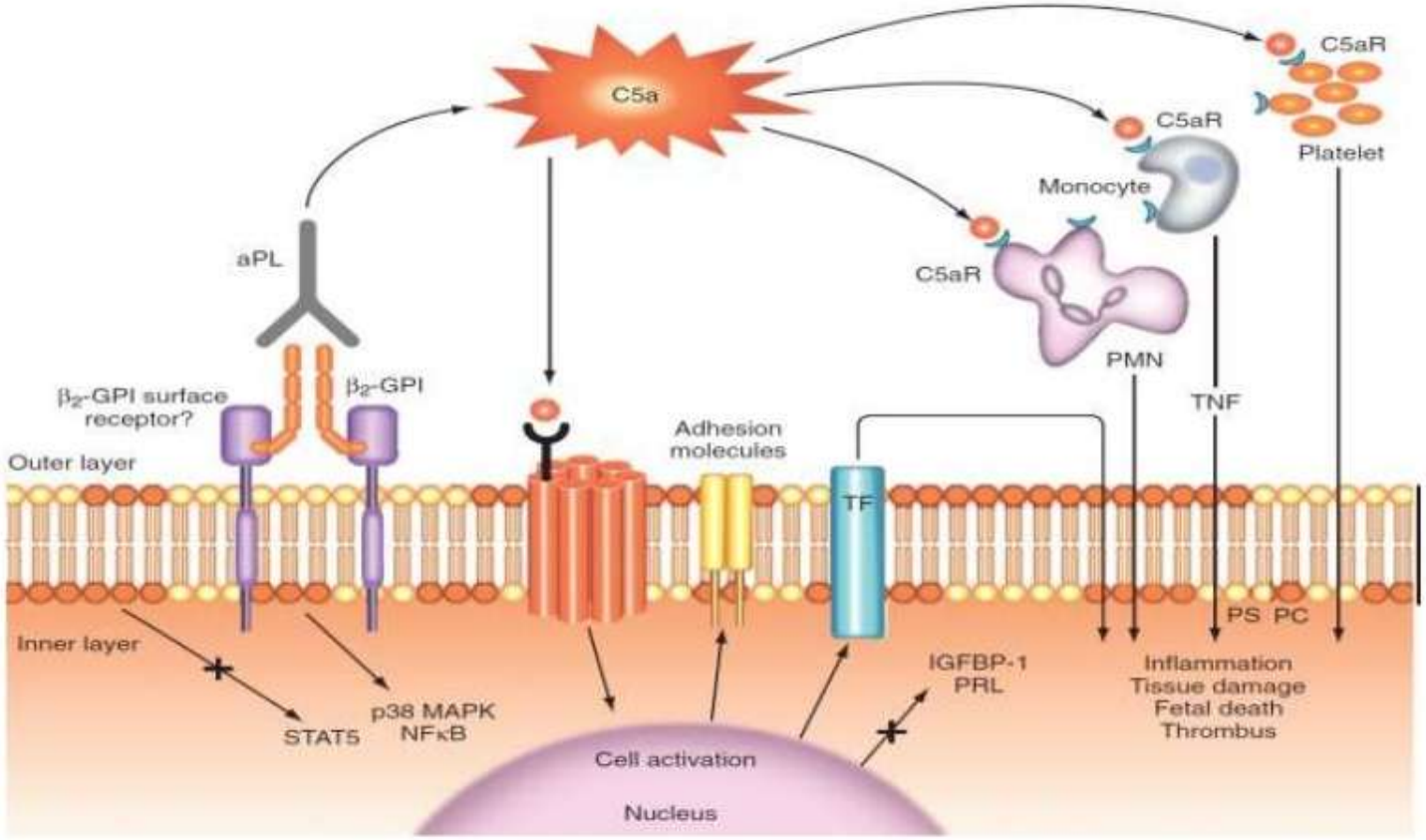
Livedo reticularis with necrotic finger t
Antiphospholipid syndrome

Possible Clinical presentation of APS

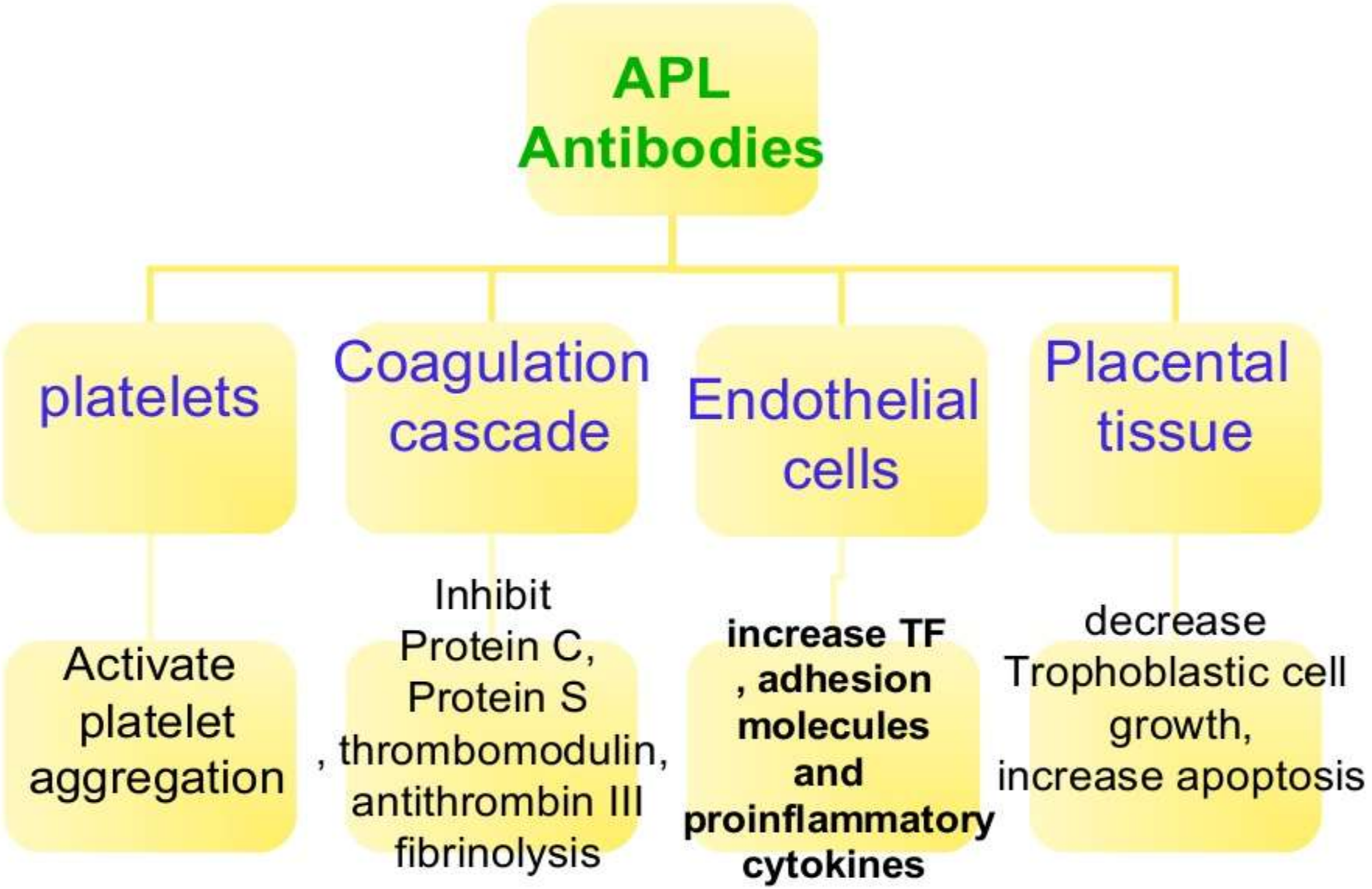
not included in criteria

- Transverse Myelitis
- Migraine
- Chorea
- Leg ulcers
- UBOs (white matter lesions) on brain MRI

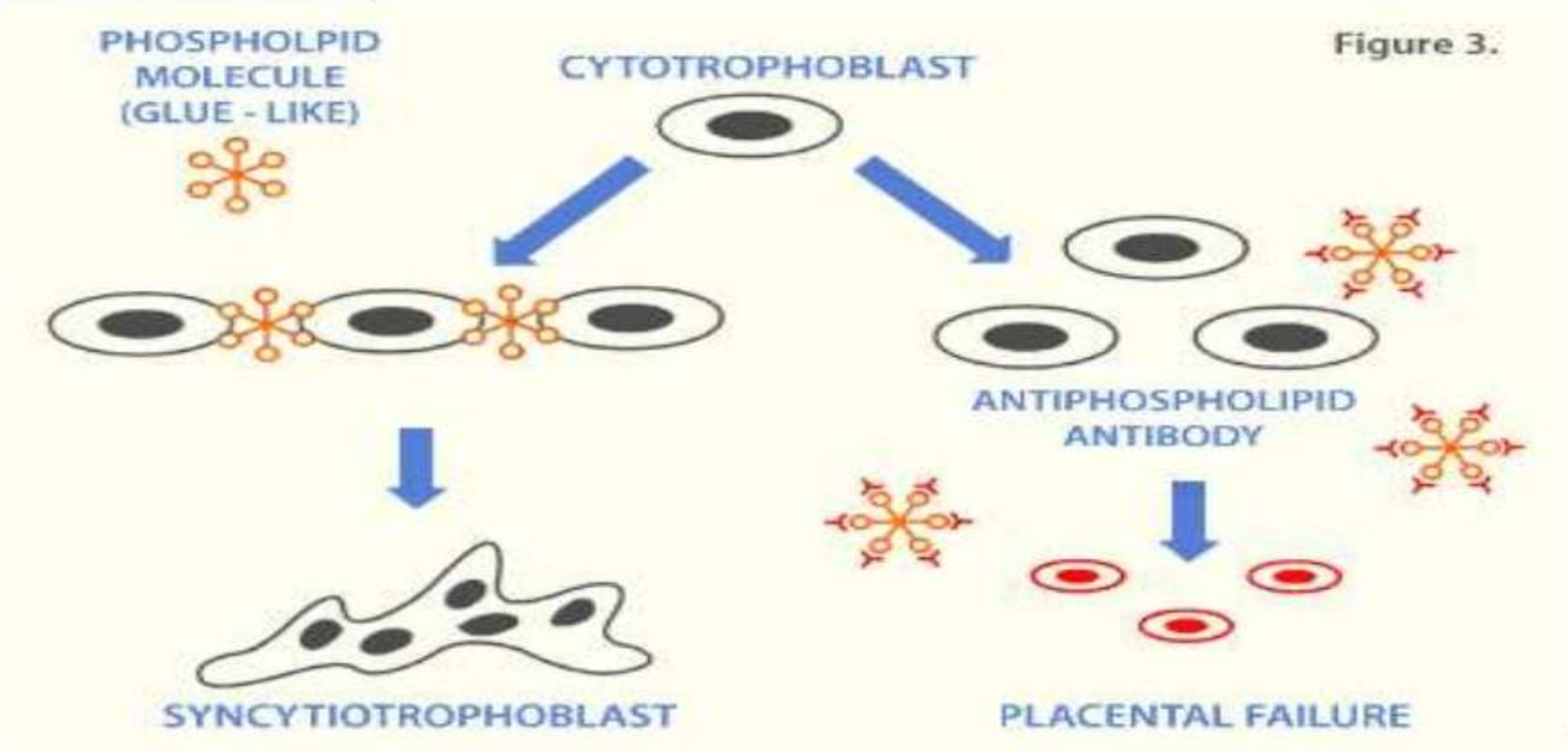
Pathogenesis



Pathophysiology



In pregnancy



Box 5 : Currently recommended treatments for antiphospholipid syndrome

Clinical Manifestations	Treatment for thrombosis prevention
Vascular Events	
Asymptomatic[a] aPL- positive patients	No treatment[b]
Venous thrombosis	Warfarin (INR: 2.0–3.0)
Arterial thrombosis	Warfarin (INR: 3.0)[c]
Recurrent thrombosis	Warfarin (INR: 3.0–4.0) + low-dose aspirin (LDA)
Catastrophic APS	Anticoagulation + corticosteroids + IVIG or plasmapheresis

Thrombocytopenia

- Mild to moderate- Platelets > 50,000:
  No treatment

- Severe- <50,000:

  - corticosteroids
  - corticosteroid resistant cases:

    HCQ , IVIG, Immunosuppressive drugs, Splenectomy

Current Recommendations

Pregnancy	Fetal protection
▶ Asymptomatic aPL	no treatment
▶ Single loss <10wks	no treatment
▶ Recurrent loss* <10wks	prophylactic heparin +ASA up to 6-12 wks postpartum, ASA after(?)
▶ Recurrent loss < 10 wks + thrombosis	therapeutic heparin + ASA, warfarin postpartum
▶ Prior thrombosis	therapeutic heparin + ASA warfarin postpartum

C
A
P
S

The "catastrophic" variant of the antiphospholipid syndrome was described by Ronald Asherson in 1992 as a condition characterized by multiple vascular occlusive events, usually affecting small vessels and developing over a short period.

Although fewer than 1% of patients with APS develop this complication, its potentially lethal outcome underlines its importance in clinical medicine today.

The majority of patients with catastrophic APS end up in intensive care units with multiorgan failure and, unless the condition is considered in the differential diagnosis by attending physicians, it may be completely missed, resulting in a disastrous outcome

criteria for the classification of catastrophic

1- Evidence of involvement of ≥ three organs, organ systems or tissues (usually confirmed by imaging techniques; renal involvement defined as a 50% rise in creatinine; severe arterial hypertension or proteinuria)

2- Development of manifestations simultaneously or within 1 week

3- Confirmation by histology of small vessel occlusion in at least one organ or tissue (confirmation of thrombosis is necessary; at times vasculitis may coexist)

4- Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)

Definite diagnosis = 4 criteria

Probable diagnosis = any of the following:

2 + 3 + 4 criteria and involvement of two organs, organ systems or tissues

1 + 2 + 3 criteria (without confirmation of APS due to early death of a patient never tested for APA before catastrophic APS

1 + 3 + 4 criteria and the development of a 3rd event between 1 week and 1 month after presentation, despite anticoagulation

Catastrophic Antiphospholipid Syndrome

- Prior history of APS in 50% to 70%.
- Precipitating factors are found in 22%.
- Infections
- Trauma
- surgical procedures
- tissue biopsies
- pregnancy and post fetal demise
- Malignancy
- ***withdrawal from anticoagulation***.

Precipitating factors according to the analysis of 250 patients from the "CAPS Registry"

Unknown	40%
Infections	22%
Trauma	14%
Anticoagulation problems	7.2%
Neoplasia	6.8%
Obstetric	4.6%
Lupus "flares"	3%

Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients.

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Main organ involved, no. (%)†	
Kidney	180 (70.6)
Lung	163 (63.9)
Brain	158 (62)
Heart	131 (51.4)
Skin	128 (50.2)
Liver	85 (33.3)
Intestine	60 (23.5)
Peripheral veins (thrombosis)	59 (23.1)
Spleen	48 (18.8)
Adrenal gland	33 (12.9)
Peripheral arteries (thrombosis)	27 (10.6)
Pancreas	19 (7.5)
Retina	17 (6.7)
Peripheral nerve	12 (4.7)
Bone marrow	10 (3.9)

Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients.

Table 1. Demographic, clinical, and laboratory features of 250 patients with CAPS*

Demographics	
Sex, no. female/no. male	177/73
Age at the time of CAPS, mean ± SD years	37 ± 14
Diagnosis, no. (%) of patients	
Primary APS	116 (46.4)
SLE	100 (40)
SLE-like	12 (4.8)
Other	22 (8.8)
No. (%) with precipitating factors†	143 (56)
No. (%) with CAPS as the first manifestation of APS	116 (46.4)

Table 2. Major cause of death and findings of histopathologic studies in patients with CAPS*

	No. (%) of patients with CAPS
Major cause of death (n = 81)	
Cerebral involvement	22 (27.2)
Stroke	15 (18.5)
Cerebral hemorrhage	4 (4.9)
Encephalopathy	3 (3.7)
Cardiac involvement	16 (19.8)
Cardiac failure	14 (17.3)
Arrhythmias	2 (2.5)
Infection	16 (19.8)
Bacterial sepsis	10 (12.3)
Fungal sepsis	3 (3.7)
Pneumocystis carinii pneumonia	2 (2.5)
Suppurative peritonitis	1 (1.2)
Multiple organ failure	14 (17.3)
Pulmonary involvement	8 (9.9)
Acute respiratory distress syndrome	6 (7.4)
Pulmonary embolism	1 (1.2)
Pulmonary hemorrhage	1 (1.2)
Abdominal involvement	4 (4.9)
Liver failure	3 (3.7)
Acute abdomen	1 (1.2)

Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Autopsies

Histopathologic features (n = 58)	
Microthrombosis	49 (84.5)
Kidney	32 (65.3)
Heart	27 (55.1)
Lung	24 (48.9)
Brain	24 (48.9)
Spleen	12 (24.5)
Skin	11 (22.4)
Gut	10 (20.4)
Liver	10 (20.4)
Adrenal gland	8 (16.3)
Infarction	31 (53.4)
Brain	19 (61.3)
Heart	9 (29)
Spleen	6 (19.4)
Kidney	5 (16.1)
Lung	5 (16.1)
Adrenal gland	3 (9.7)
Thrombosis of large vessels	11 (18.9)
Pulmonary embolism	7 (12.1)
Nonbacterial thrombotic endocarditis	16 (27.6)
Acute respiratory distress syndrome	4 (6.8)
Alveolar hemorrhage	3 (5.2)
Budd-Chiari syndrome	1 (1.7)
Adrenal hemorrhage	1 (1.7)

Distinct differences of patients with catastrophic APS

- Unusual organs affected (eg, ovaries, uterus, testes)
- ARDS
- Early loss of consciousness
- DIC
- Abdominal pain : intra-abdominal vascular complications
- Severe thrombocytopenia
- HELLP syndrome
- Poor prognosis

Catastrophic Antiphospholipid Syndrome

- ***Valvular vegetations.***
- ***Coronary artery occlusion*** with cardiac failure and circulatory collapse.
- ***Thrombus formation within the cardiac chambers.***

aPL-associated cardiac valve

Regurgitation* *and/or* stenosis of mitral *and/or* aortic valve or any combination of the above.

Valve examination can be performed with TTE and/or with TEE

Defining valve lesions include:

Valve thickness > 3 mm,

Localized thickening involving the leaflet's proximal or middle portion,

Irregular nodules on the atrial face of the edge of the mitral valve, *and/or* the vascular face of the aortic valve.

endocarditis

Renal Manifestations

Hypertension, renal artery stenosis (RAS)
Thrombotic microangiopathy (TMA)
APS nephropathy (APSN)
Venous renal thrombosis
APSN in the course of SLE and renal failure
Cortical ischaemia/infarction
End-stage renal failure and renal transplantation

APL-associated nephropathy (APLN)

Thrombotic microangiopathy involving both arterioles and glomerular capillaries *and/or*

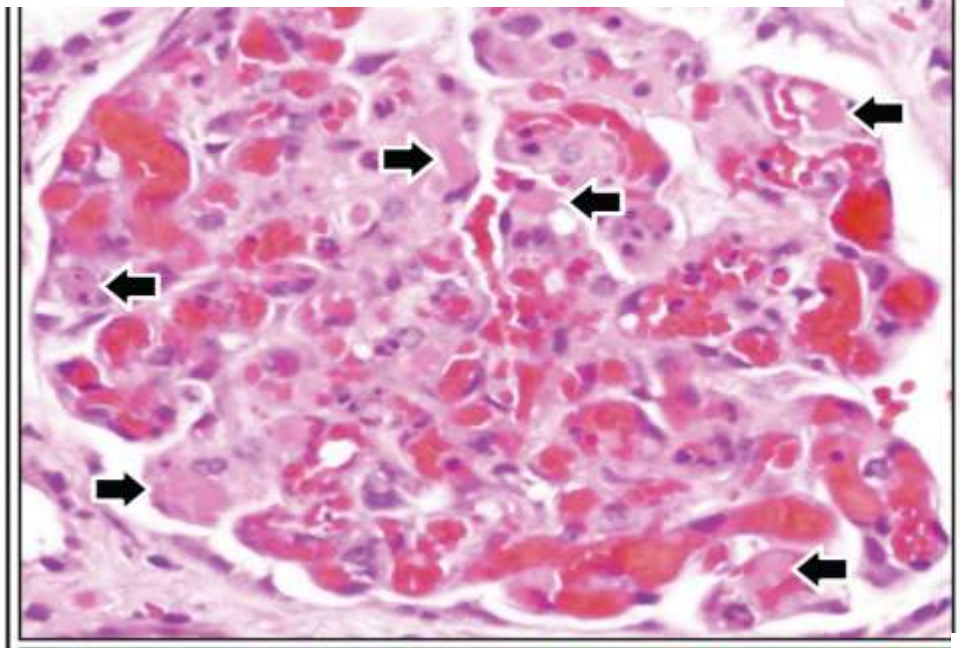
One or more of:

- Fibrous intimal hyperplasia involving organized thrombi with or without recanalization
- Fibrous and/or fibrocellular occlusions of arteries and arterioles
- Focal cortical atrophy
- Tubular thyroidization (large zones of atrophic tubules containing eosinophilic casts)

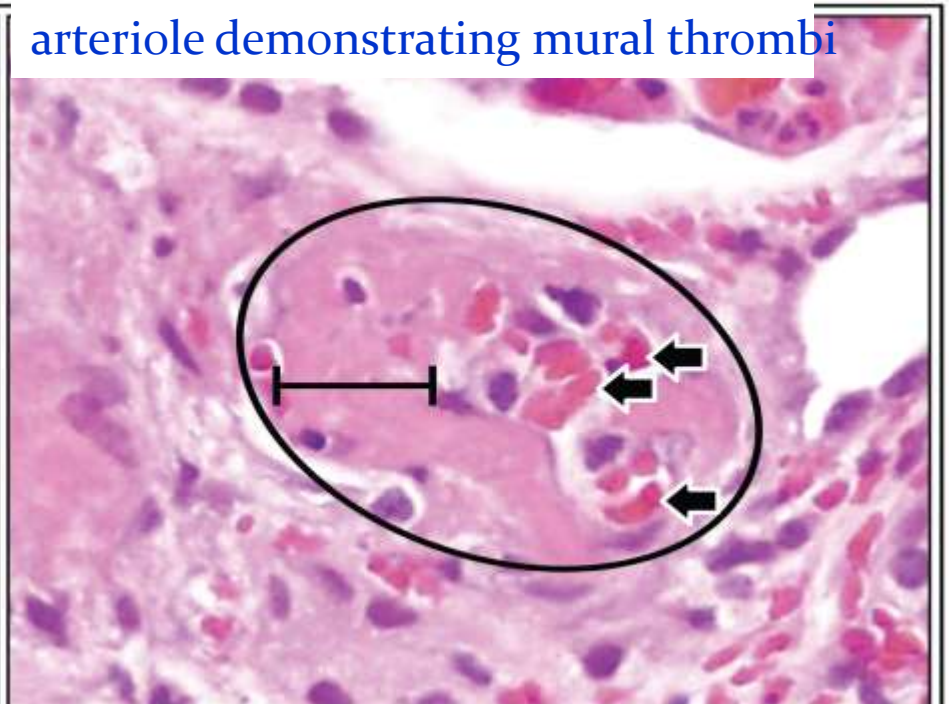
Catastrophic Antiphospholipid Syndrome

- ***Renal thrombotic microangiopathy of the glomerular capillaries and small renal arteries.***

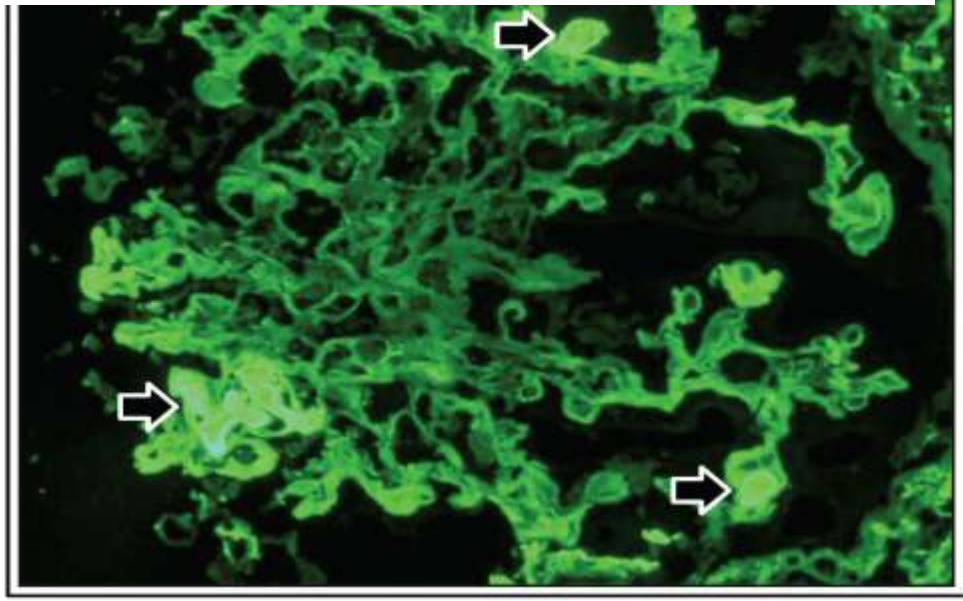
glomerulus congestion and microthrombi



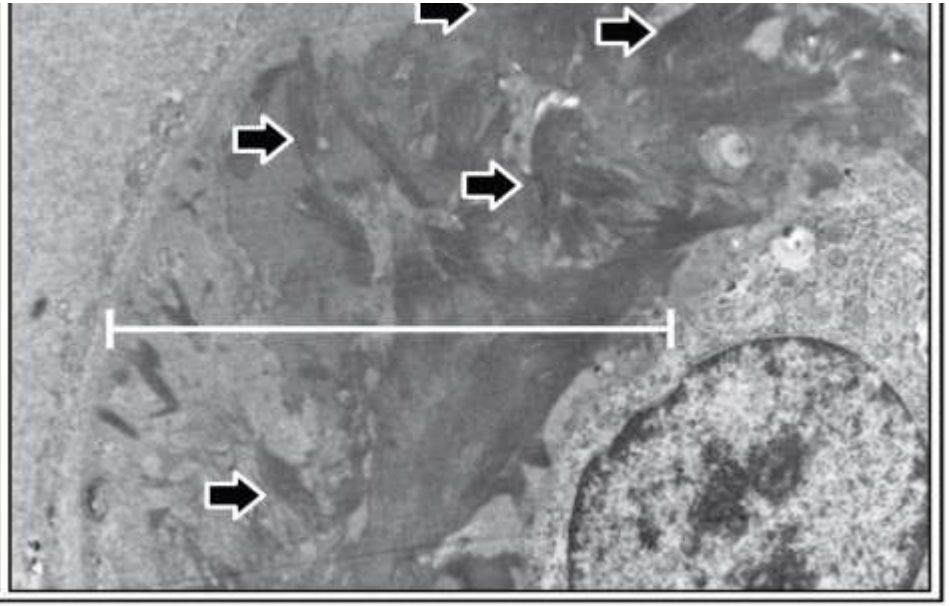
arteriole demonstrating mural thrombi



several fibrin thrombi in glomerulus
immustaining



fibrin tactoids in the expanded subendothelial space of a glomerular capillary



PULMONARY

- Lung syndrome –

pulmonary microthrombosis, PTE , PAH, ARDS intra alveolar hemorrhage and postpartum syndrome

CNS

- Stroke in young
  Singh K, Shome DK et al - 18.8 %

- Sneddon 's syndrome – livedo reticularis ,stroke and CVA
- Non thrombotic neurologic symptoms like focal neurologic manifestations

- Multiple hyperintense lesions in a MRI in young ind. < 40
- Siezures

- CSVT , Multi infarct dementia , migraine headache,GB Syndrome ,chorea and optic neuritis

GIT

- Budd-chiari syndrome
- Intestinal ischemia and infarction
- Colonic ulceration
- Esophageal necrosis and perforation
- Hepatic infarction
- Mesentric and portal vein thrombosis

Treatment for CAPS

1. Prophylactic therapy
2. Specific therapies
3. Nonspecific therapies : ICU

Specific therapies

- ***First-line therapies***
- **Intravenous heparin**

(1500 U/h) 7 - 10 days

followed by oral **anticoagulants** (INR 3)

- **Corticosteriods**

(1-2 mg/kg/day) :

minimum 3 days

- ***Second-line therapies***
- Intravenous immunoglobulins
- Plasma exchange
- Cyclosphosphamide
- Rituximab
- Prostacyclin
- Other fibrinolytics

Prophylactic therapy

1. Any infection, however trivial, should be energetically treated with the appropriate antibiotics.
2. APS patients undergoing surgical procedures, however minor, should all receive parenteral anticoagulation during the procedure instead of remaining on coumadin.
3. The puerperium should be adequately covered for a minimum of 6 weeks with parenteral anticoagulants (eg, subcutaneous heparin).
4. SLE "flares," although uncommonly associated with catastrophic APS, should also be treated with parenteral anticoagulation.

Recommendations for perioperative medical

Preoperative assessment

- Prolonged activated partial thromboplastin time or slightly prolonged prothrombin time when known to be due to APS are *not* contraindications for surgical procedures
- Platelet count >100 × 10^9/L due to APS requires no specific therapy; thrombocytopenia does not protect against thrombosis
- Surgical and interventional procedures should be the last option in the management of patients with APS

Recommendations for perioperative medical management of patients with APS

Perioperative considerations

- Minimize intravascular manipulation for access and monitoring
- Set pneumatic blood pressure cuffs to inflate infrequently to minimize stasis in the distal vascular bed
- Avoid tourniquets
- Maintain high suspicion that any deviation from a normal course may reflect arterial or venous thrombosis

Recommendations for perioperative medical

Perioperative anticoagulation

- Keep periods without anticoagulation to an absolute minimum
- Employ pharmacologic and physical antithrombosis interventions vigorously and start immediately before the operation, continuing until the patient is fully ambulating
- Be aware that patients with APS can develop recurrent thrombosis despite appropriate prophylaxis
- Be aware that current conventional doses of antithrombotic regimens can result in "underanticoagulation"; patients with APS may benefit from an aggressive approach with higher than standard doses
- Manage patients with APS whose only clinical manifestation is pregnancy morbidity as if they had vascular thrombosis

TAKE HOME MESSAGE

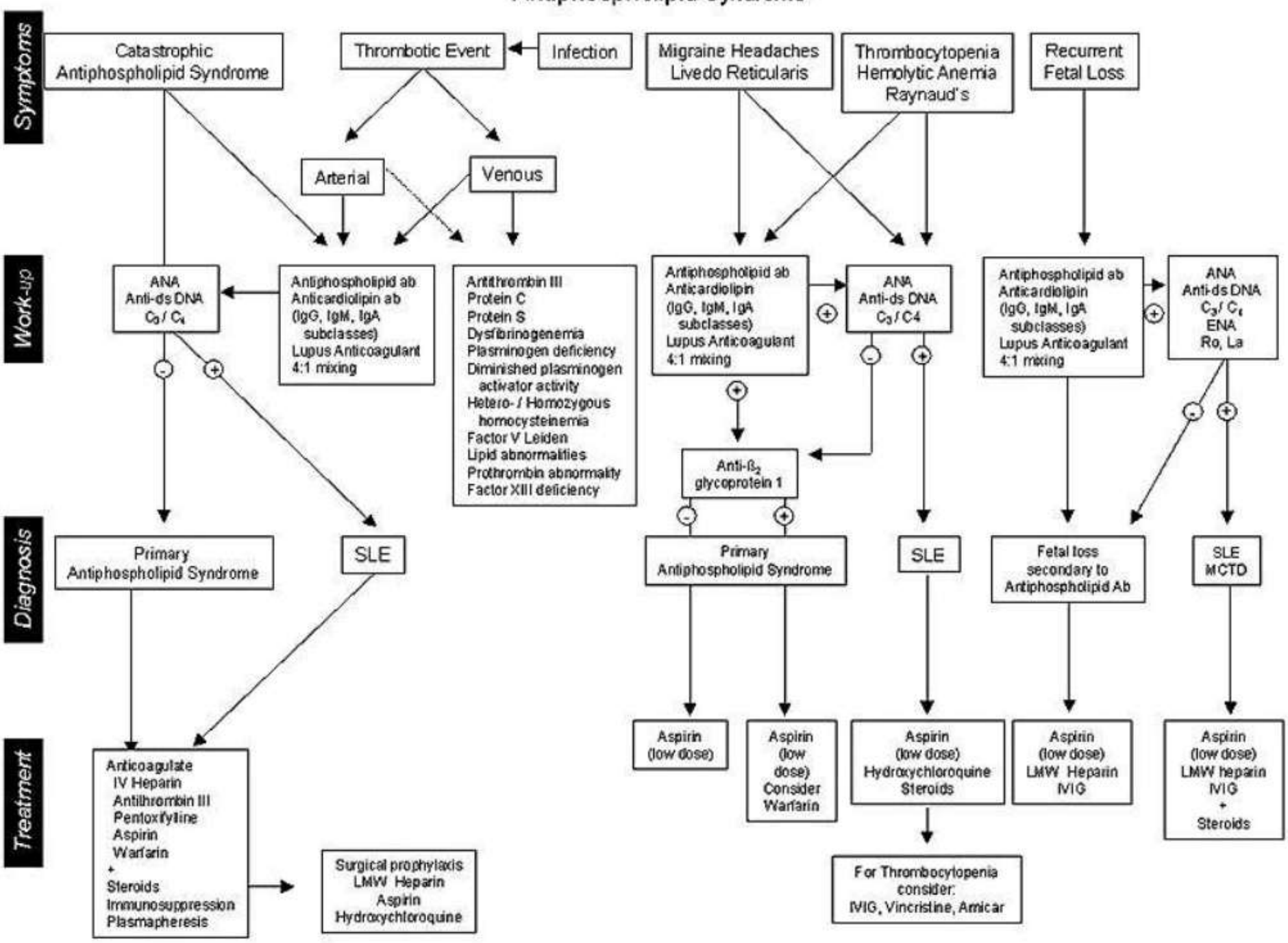
- *Think of APLS in a young female with thrombosis,fetal wastage.*
- *Recurrent migraine headaches in a young female –do APL*
- *INR to be individualized and mainatined at 2.0-3.0*
- *Recurrent –3.0-4.0*

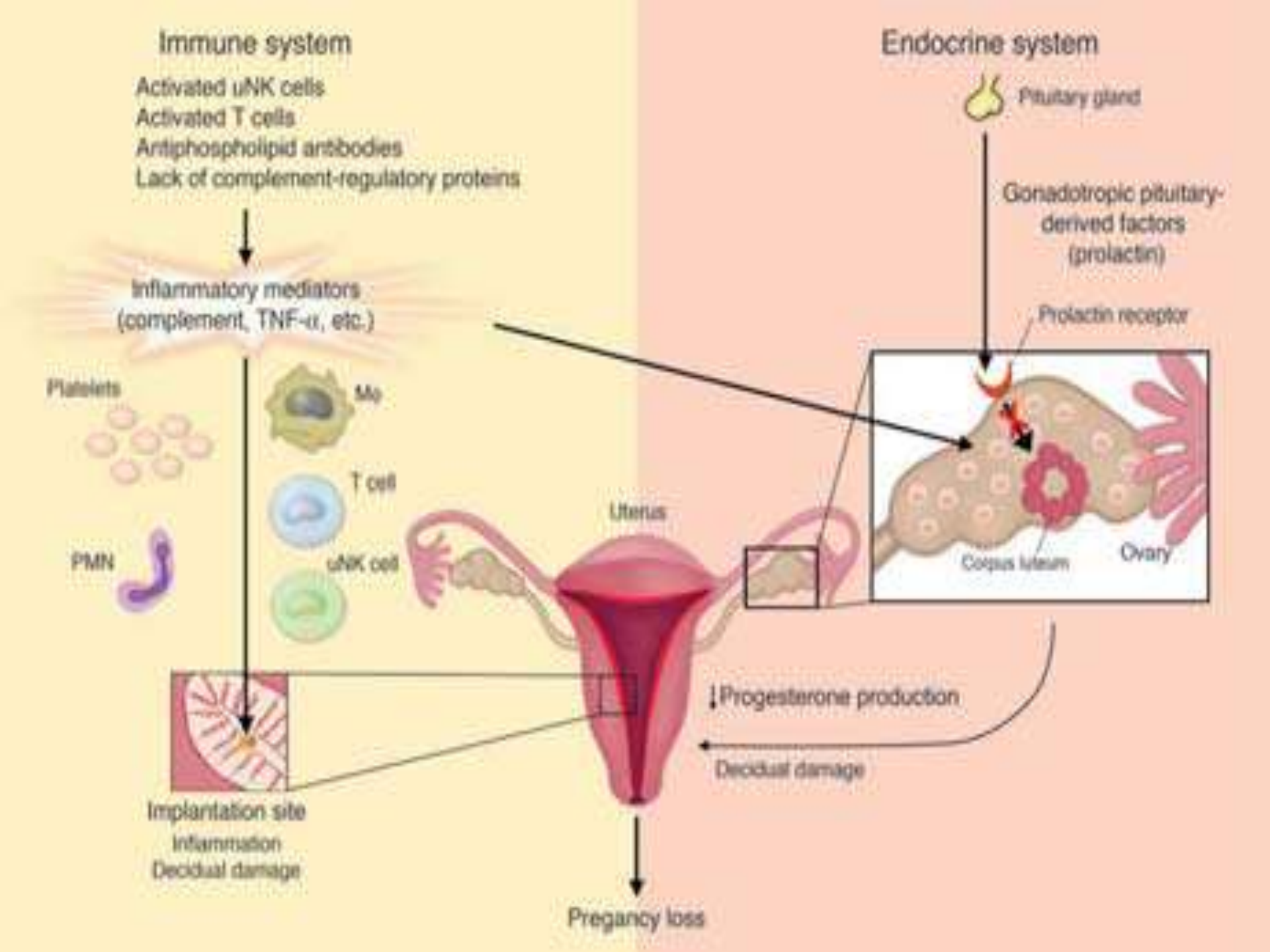
Recognize the condition early,at the same time avoiding overdiagnosing this condition, as the treatment in unwarranted situations can be hazardous

THANK YOU

Catastrophic antiphospholoipid syndrome

- **Treatment: 2003 International Consensus Statement on CAPS**
- **Rx recommendation:**
- Anticoagulants (AC)
  - iv heparin, 7-10 days
  - Warfarin, INR ~3
- Corticosteroids (CS)
  - for a minimal of 3 days, further Rx depending on patient's response
- Plasma exchange (PE)
- And /or IVIG
- **AC + CS – most common therapy used**
- **AC + CS + PE and/or IVIG – 2nd most common** regimen
- Therapeutic regimen combining anticoagulation, corticosteriods and plasma exchange has the best recovery rate (77.8%)


Antiphospholipid Syndrome
Symptoms
Work-up
Diagnosis
Treatment
Catastrophic Antiphospholipid Syndrome
Thrombotic Event
Infection
Migraine Headaches Livedo Reticularis
Thrombocytopenia Hemolytic Anemia Raynaud's
Recurrent Fetal Loss
Arterial
Venous
ANA Anti-ds DNA C3 / C4
Antiphospholipid ab Anticardiolipin ab (IgG, IgM, IgA subclasses) Lupus Anticoagulant 4:1 mixing
Antithrombin III Protein C Protein S Dysfibrinogenemia Plasminogen deficiency Diminished plasminogen activator activity Hetero- / Homozygous homocysteinemia Factor V Leiden Lipid abnormalities Prothrombin abnormality Factor XIII deficiency
Antiphospholipid ab Anticardiolipin (IgG, IgM, IgA subclasses) Lupus Anticoagulant 4:1 mixing
ANA Anti-ds DNA C3 / C4
Antiphospholipid ab Anticardiolipin (IgG, IgM, IgA subclasses) Lupus Anticoagulant 4:1 mixing
ANA Anti-ds DNA C3 / C4 ENA Ro, La
Anti-ß2 glycoprotein 1
Primary Antiphospholipid Syndrome
SLE
Primary Antiphospholipid Syndrome
SLE
Fetal loss secondary to Antiphospholipid Ab
SLE MCTD
Anticoagulate IV Heparin Antithrombin III Pentoxifylline Aspirin Warfarin + Steroids Immunosuppression Plasmapheresis
Surgical prophylaxis LMW Heparin Aspirin Hydroxychloroquine
Aspirin (low dose)
Aspirin (low dose) Consider Warfarin
Aspirin (low dose) Hydroxychloroquine Steroids
Aspirin (low dose) LMW Heparin IVIG
Aspirin (low dose) LMW heparin IVIG + Steroids
For Thrombocytopenia consider: IVIG, Vincristine, Amicar


Immune system
Activated uNK cells
Activated T cells
Antiphospholipid antibodies
Lack of complement-regulatory proteins
Inflammatory mediators
(complement, TNF-α, etc.)
Platelets
Mφ
T cell
PMN
uNK cell
Implantation site
Inflammation
Decidual damage
Endocrine system
Pituitary gland
Gonadotropic pituitary-derived factors (prolactin)
Prolactin receptor
Uterus
Corpus luteum
Ovary
↓Progesterone production
Decidual damage
Pregancy loss

Potential current and future treatments for antiphospholipid syndrome

Future
GPIIb/IIIa-specific antagonists
p38MAPK inhibitors
Thromboxane A2 inhibitors
Tissue factor expression inhibition
Complement inhibition
Synthetic peptides
βGPI toleragen
New anticoagulants in development

CAPS/GB/Nice2007


Manger, Erlangen

Laboratory Findings in CAPS

Anticardiolipin IgG	83%
Lupus anticoagulant	82%
Antinuclear antibodies	66%
Thrombocytopenia	46%
Anticardiolipin IgM	38%
Hemolytic anemia	35%
Schistocytes on blood film	16%
Acute-phase proteins	?

Activated protein C resistance
Antiphospholipid antibody syndrome
Antithrombin III deficiency
Dysfibrinogenemia
Hageman factor deficiency
Homocystinuria
Hypercoagulable state of patients taking certain medications(eg, oral contraceptives, heparin)
Plasminogen and plasminogen-activator deficiency
Protein C and S deficiency

Hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are characterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic injury to organs
While fever and neurologic manifestations frequently dominate the clinical picture in TTP, most patients with HUS suffer from renal disease.

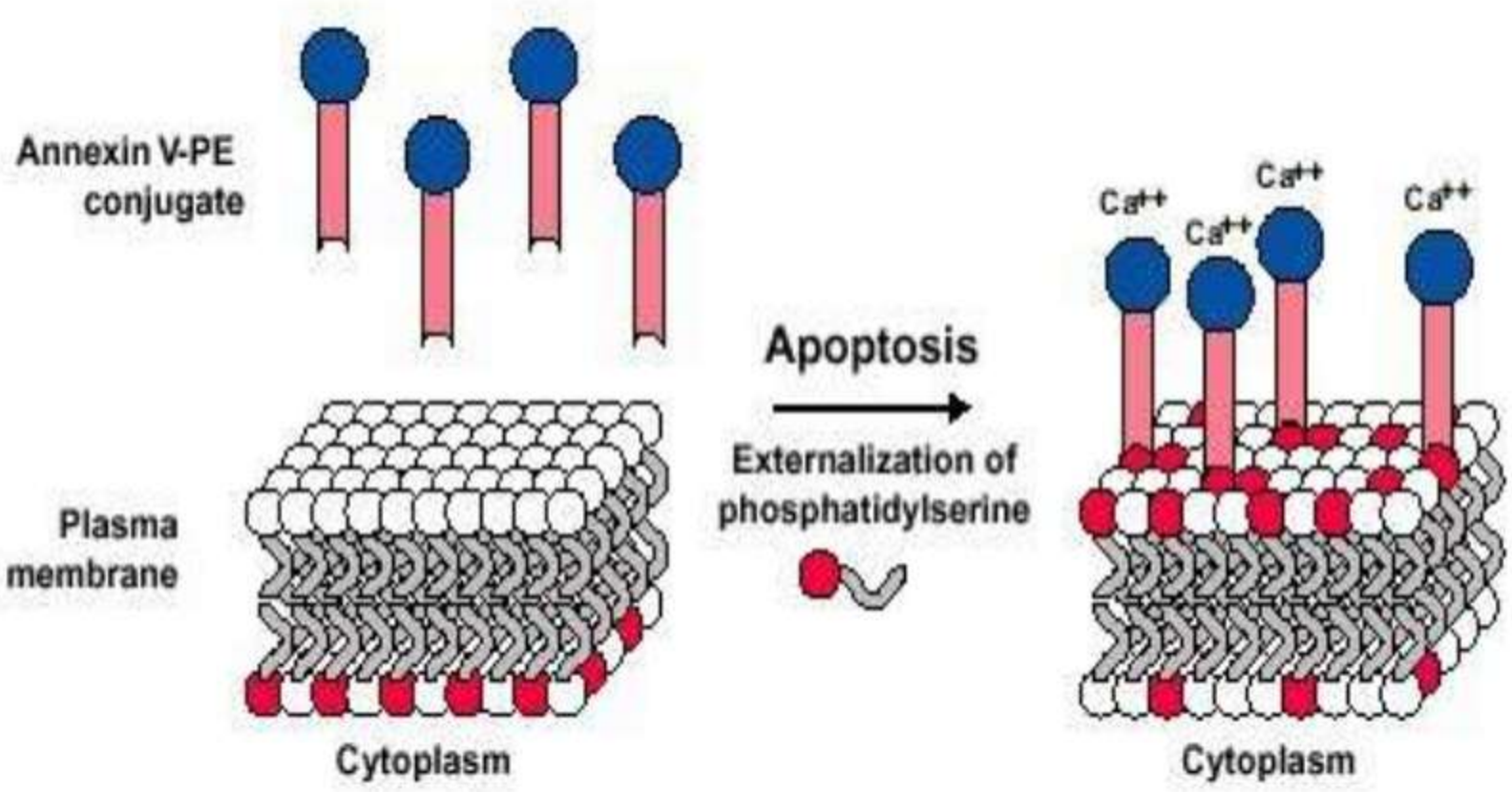
As a general rule, thrombocytopenia and schistocytosis are marked in HUS/TTP and mild, or even absent, in CAPS. Activated partial thromboplastin time is usually normal in HUS/TTS, but it may be elevated in CAPS in the presence of lupus anticoagulant. Whereas the presence of antiphospholipid antibodies is the serological hallmark of CAPS

Although CAPS is primarily due to vascular thrombosis, DIC usually manifests signs of thrombosis and bleeding at the same time. Nonetheless, DIC may complicate CAPS in one third of patients.

Catastrophic Antiphospholipid Syndrome

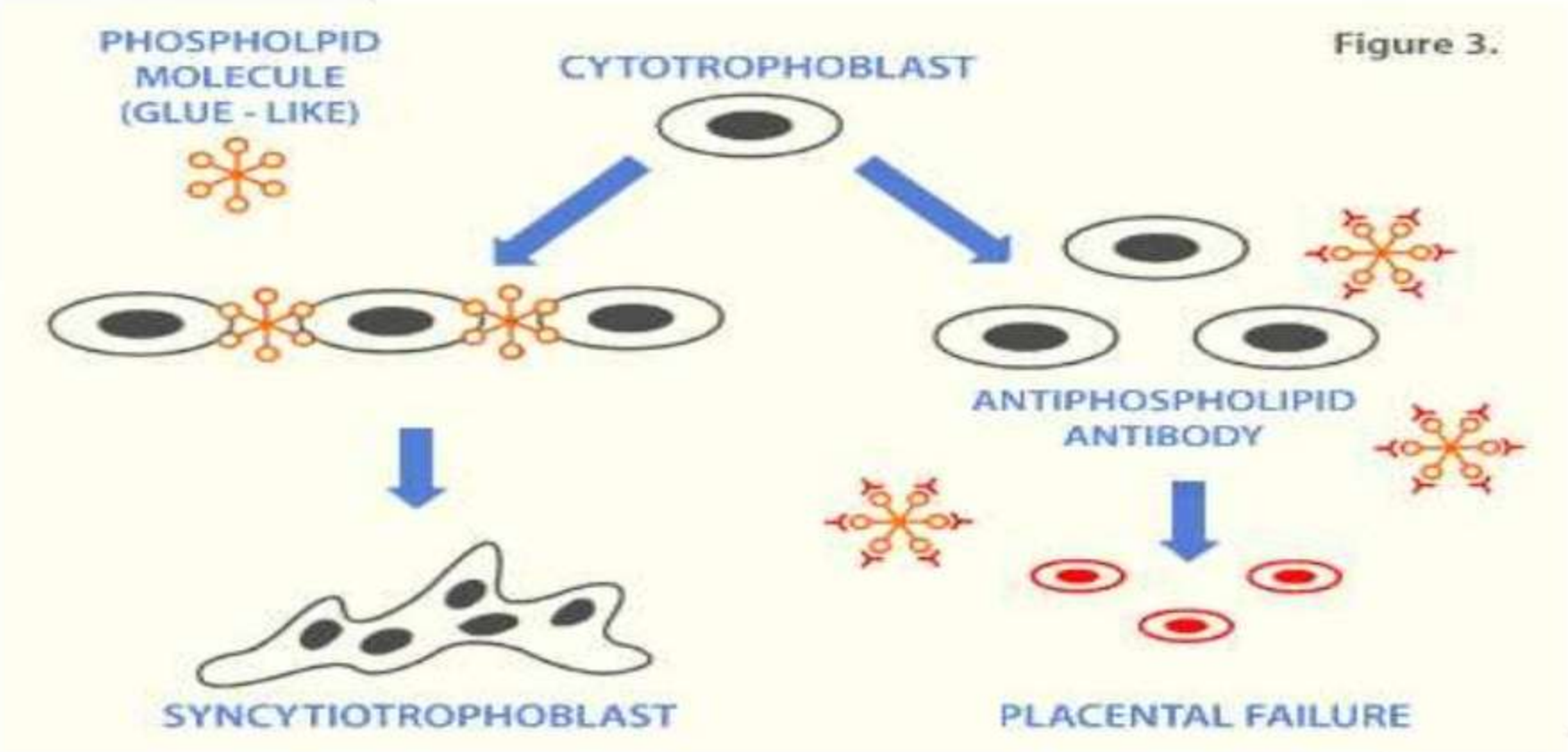
- Diffuse injury to the capillary endothelial and epithelial cells resulting in ***ALI and ARDS***.
- Microvascular thrombi causing endothelial damage, neutrophil influx and cytokines release.
- ***Alveolar hemorrhage*** **.**

Annexin V



Schematic representation of the Annexin V assay.

In pregnancy



Diluted Russells viper venom test

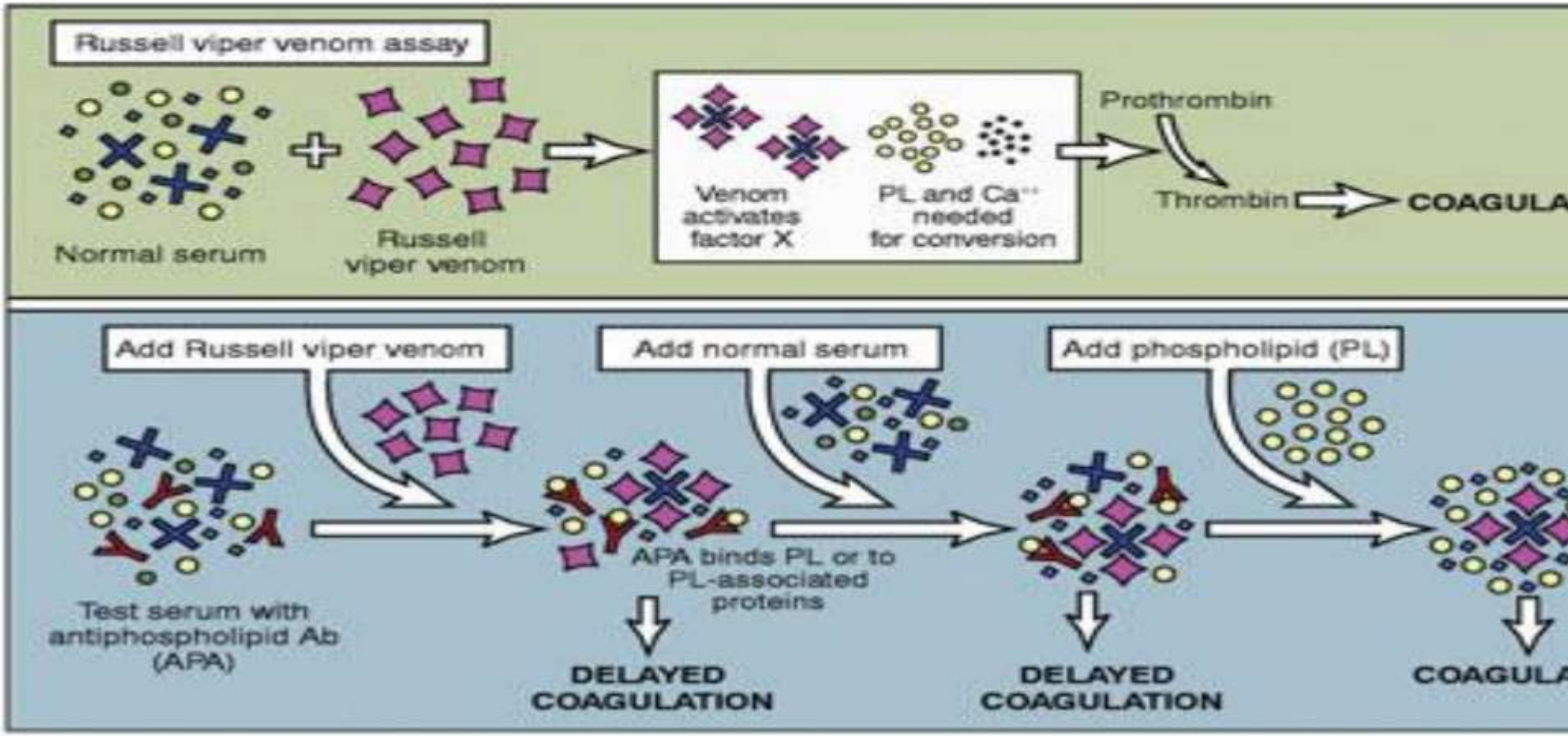


Figure 2. Antiphospholipid antibody determination of LA by the dRVVT.

28-year-old woman presents with a history of 2 first-trimester miscarriages and no live births. She is considering trying to become pregnant but is concerned about her risk for another miscarriage. Otherwise, her medical history is negative.

You consider whether this woman has antiphospholipid syndrome (APS). Which of the following is part of the Sapporo criteria for the diagnosis of APS?
At least 2 previous pregnancies with significant intrauterine growth retardation
At least 2 unexplained abortions at less than 10 weeks' gestation
The presence of anticardiolipin antibodies on any blood sample
History of arterial thrombosis

Putative Pathogenic Mechanisms in CAPS

Cellular activation

- Endothelial cell activation
- Immune cell activation
- Platelet activation

Inhibition of anticoagulants

- Inhibition of the protein C pathway
- Disruption of annexin A5 shield

Inhibition of fibrinolysis

- Inhibition of plasminogen activator inhibitor-1
- Blocking of β^2-glycoprotein I
- Blocking of annexin A2

Complement activation

- Endothelial cell activation by C5a and MAC
- Immune cell activation by C5a
- Platelet activation by C3a and MAC

- Inhibition of fibrinolysis by C5a

TAKE HOME MESSAGE

- *Think of APLS in a young female with thrombosis,fetal wastage.*
- *Recurrent migraine headaches in a young female –do APL*
- *INR to be individualized and mainatined at 2.0-3.0*
- *Recurrent –3.0-4.0*